same target nucleic acid, wherein each unique oligonucleotide hybridizes to a different region of said target nucleic acid of the probe oligonucleotide spot.

58. (Amended) An array comprising a pattern of probe oligonucleotide spots each having a diameter ranging from about 50 to 500μ of a density that does not exceed about 400 spots/cm^2, wherein each probe oligonucleotide spot comprises an oligonucleotide probe composition made up of 3 to 20 unique oligonucleotides of different sequence and from about 25 to 100 nucleotides in length that hybridize to the same target nucleic acid, wherein each unique oligonucleotide hybridizes to a different region of the said target nucleic acid.

REMARKS

I. Interview

The undersigned thanks the Examiner for the courteous and helpful interview which was held on November 2, 2000. During the interview, the claim terminology was discussed with respect to the cited prior art. Specifically, the term "spot" of the presently pending claims was discussed with respect to the disclosure of a "cell" in the cited Brown reference. In addition, the Examiner explained her reading of the cited Fodor reference and its impact on the patentability of the presently pending claims. Finally, the Examiner suggested that evidence demonstrating unexpected results be submitted in order to move the application in condition for allowance. The requested unexpected results are provided in the enclosed declaration and are discussed at the end of this response.

II. AMENDMENTS.

In view of the above amendments and the following remarks, the Examiner is requested to withdraw the rejections and allow Claims 1-17, 53, and 57-59, the only claims pending and currently under Examination in this application.

Claims 1, 57 and 58 have been amended to limit the arrays to ones in which each oligonucleotide probe composition of each probe spot has a diameter ranging from about 50

to 500μ. Support for this amendment can be found in the specification at page 12, line 11. As such, the above amendments introduce no new matter to the application and their entry by the Examiner is respectfully requested.

III. REJECTIONS.

A. Rejection Under 35 U.S.C. § 102.

In the Final Rejection, the rejection of Claims 1, 2, 5-10, 12-17, and 57-58 under 35 U.S.C. § 102 as being anticipated by Brown et al (U.S. Pat. No. 5,807,522) has been maintained. In maintaining this rejection, the Examiner has equated the term "spot" of the presently pending claims with the disclosed "cell" of the Brown arrays. In other words, the Examiner has equated the Brown disclosed microarray of each cell in Brown's multicell array with a spot of the presently claimed arrays.

Initially, it is respectfully submitted that the Examiner is incorrectly equating the spots of the presently claimed arrays with the cells of Brown's multicell arrays. The spots of the presently claimed arrays correspond to Brown's individual regions, i.e. the individual components that make up each of Brown's microarrays. The spots of the present arrays are clearly equal to Brown's regions in view of the specification of the present application, which discloses on page 10, lines 15 to 27, array embodiments that are made of a plurality of oligonucleotide spot patterns, where each oligonucleotide spot pattern is the same as the microarray of Brown. As such, it is respectfully submitted that it is incorrect to equate the probe spots of the claimed arrays with the Brown's cells, as the Examiner has done in maintaining this rejection.

Nevertheless and solely in order to expedite prosecution of the present application to allowance, the arrays have been amended to limit the probe spots of the claimed arrays to ones that have a diameter ranging from about 50 to 500μ. This limitation clearly

distinguishes the present arrays over Brown's arrays because Brown teaches that the width of the cells ranges from 1 to 20 mm and the length of the cells ranges from 1 to 50 mm. See Col. 11. lines 66-67.

Therefore, Brown clearly fails to teach or suggest the claimed arrays because Brown fails to teach or suggest oligonucleotide probe compositions having a diameter ranging from about 5 to 50 μ, even when the claimed probe spots are equated to Brown's disclosed microarray comprising cells. Because the diameter limitation of the claimed invention is not taught by Brown, Brown fails to anticipate the claimed invention.

In sum, Claims 1, 2, 5-10, 12-17, and 57-58, which require each oligonucleotide spot to have a diameter ranging from about 50 to 500μ are not anticipated by Brown et al because Brown does not teach this limitation. Accordingly, Claims 1, 2, 5-10, 12-17, and 57-58 are not anticipated under 35 U.S.C. § 102 over Brown and this rejection may be withdrawn.

B. Rejection Under 35 U.S.C. § 103.

Claims 3-4 have been rejected under 35 U.S.C. § 103(a) over Brown et al in view of Fodor et al. (U.S. Pat. No. 5,800,992, filed June 25, 1996) for the asserted reason that Brown teaches all of the limitations of the claimed invention except for the placement of the probes on the array corresponding to non-overlapping or overlapping regions of a target nucleic acid, which is assertedly supplemented by the Fodor et al. reference.

The M.P.E.P. teaches that a proper *prima facie* case requires that a combined teaching of two or more references must teach or suggest all the claim limitations. The M.P.E.P. states in relevant part:

> "To establish a prima facie case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success.

Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations." M.P.E.P. § 2142.

Thus, in order for a proper *prima facie* case to made, the combined teachings of the cited references must teach or suggest all of the limitations of the claims.

In the present application, the Applicants are claiming an array which is limited in that each polynucleotide probe spot must have a specific diameter, as explained above.

As demonstrated above, Brown fails to teach or suggest an array in which each spot must contain two or more different oligonucleotides of different sequence that hybridize to the same nucleic acid target, where the spot has a specific diameter.

For the following reasons, Fodor fails to make up this fundamental deficiency in the Brown reference. Fodor teaches that "probes of known . . . sequence may be immobilized to the matrix and a map of **various different target sequences** may be determined from overlaps." (Col. 10, lines 9-12). Thus, Fodor suggests using probes to map or determine the sequential ordering of a plurality of various sequences using probes that hybridize to various different target sequences. In other words, different probe spots on the Fodor array may include probes that hybridize to different regions of the same target nucleic acid sequence. **However, each probe spot on the Fodor array is made up of identical probes, not two or more different probes of different sequence.** As such, Fodor fails to make up the fundamental deficiency in the Brown teaching.

As such, the combined teachings of the cited references fail to teach or suggest an array of probe oligonucleotide spots where each spot contains a plurality of unique oligonucleotides of different sequence that each hybridize to the same target nucleic acid and each spot is of a specific diameter. Because this limitation of the claimed invention is neither taught nor suggested by the combined teachings of the cited references, a proper *prima facie* case of obviousness has not been established.

In sum, because the combined teachings of Brown and Fodor fail to teach or suggest an array on which each oligonucleotide probe spot contains a plurality of unique polynucleotide probes containing two or more different probes of different sequence that hybridize to the same target nucleic sequence and the spot is of a specific diameter, Claims 3-4 are not obvious under 35 U.S.C. § 103(a) over these references and this rejection may be withdrawn.

Claims 11 has been rejected under 35 U.S.C. §103(a) over Brown in view of a Lockhart et. al. (U.S. Pat. No. 6,040,138, filed June 7, 1995) for the asserted reason that Brown teaches the array of the present invention but for the element of at least one mismatch probe on the array, which this missing element is provided by the Lockhart reference. However, as demonstrated above, the Brown fails to teach or suggest the fundamental limitation that each probe spot contain at least two different oligonucleotides of different sequence that hybridize to the same target nucleic acid, where the spot is of a diameter ranging from about 50 to 500μ. As Lockhart is cited solely for his teaching of mismatch probes, this reference fails to make up this fundamental deficiency of Brown. Accordingly, Claim 11 is not obvious over Brown in view of Lockhart and this rejection may be withdrawn.

Finally, Claims 53 and 59 have been rejected under 35 U.S.C. §103(a) over Brown et al. in view of a Stratagene catalog (1988), page 39 for the asserted reason that Brown teaches arrays of the claimed invention (i.e. the array according to Claim 1) but for the motivation to combine reagents with the array to make up the kit, which missing element is provided by the Stratagene reference. However, as demonstrated above, the Brown reference fails to teach or suggest the fundamental limitation that each probe spot contain at least two different oligonucleotides of different sequence that hybridize to the same target nucleic acid, where the spot has the diameter as now claimed. As the Stratagene reference is cited solely for the teaching of kits in general, this reference fails to make up this fundamental deficiency of Brown. Accordingly, Claims 53 and 59 are not obvious over Brown in view of Stratagene and this rejection may be withdrawn.

IV. Demonstration of Unexpected Results

As mentioned above in the Interview Summary, during the interview held on November 2, 2000, the Examiner suggested that it would greatly expedite prosecution of the present application to allowance if evidence of unexpected results could be provided.

To this end, the Applicants are enclosing the attached 1.132 declaration. The attached 1.132 declaration demonstrates that the subject arrays unexpectedly provide for a hybridization signal in each spot which is unexpectedly much greater than the additive sum of the hybridization signals which would be expected. Specifically, the attached declaration provides a figure showing the hybridization signal that is achieved when probes are present in individual spots and that which is achieve under identical hybridization conditions when each of the probes are present in the same spot, as claimed in the present application. The signal resulting from the combined probe spot is unexpectedly greater than the additive signal one would expect to achieve.

Therefore, the attached declaration clearly demonstrates that unexpected results are achieved with the subject arrays.

It is hoped that submission of the attached declaration demonstrating the obtainment of unexpected results with the presently claimed arrays expedites prosecution of the present application to allowance, as suggested by the Examiner.

In view of the above amendments and remarks, this application is considered to be in good and proper form for allowance and the Examiner is respectfully requested to pass this application to issue.

The Commissioner is hereby authorized to charge any fees under 37 C.F.R. §§ 1.16 and 1.17 which may be required by this paper, or to credit any overpayment, to Deposit Account No. 50-0815.

Respectfully submitted,

BOZICEVIC, FIELD & FRANCIS LLP

Date: 12/15/00

By: _____
Bret Field
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- declaration

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